JACC Vol. 8, No. 1
July 1986:225–31

Effects of Esmolol on Patients With Left Ventricular Dysfunction

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This study examined the effect of esmolol, an ultrashort-acting beta-receptor blocker, in 10 patients with severe left ventricular dysfunction. Simultaneous hemodynamic and radionuclide angiographic measurements were obtained at incremental doses of esmolol (2, 4, 8, 12 and 16 mg/min). At a dose of 4 mg/min, esmolol produced bets blockade: a decrease in heart rate from 91 ± 4 to 83 ± 4 beats/min ($p < 0.05$) (mean ± SEM) and a decrease in systolic aortic pressure from 133 ± 5 to 128 ± 5 mm Hg ($p < 0.05$). At the maximal dose, the heart rate decreased to 79 ± 3 beats/min ($p < 0.05$) and biventricular function was depressed; the left ventricular ejection fraction decreased from 27 ± 2 to 21 ± 2% ($p < 0.05$) and the right ventricular ejection fraction decreased from 38 ± 2 to 29 ± 2% ($p < 0.05$). These changes were accompanied by increases in left ventricular end-diastolic volume ($p < 0.05$), left ventricular end-systolic volume ($p < 0.05$) and pulmonary artery wedge pressure ($p < 0.05$), as well as a decrease in cardiac output ($p < 0.05$). The hemodynamic abnormalities (which showed considerable interindividual variability) returned to near baseline levels 10 to 30 minutes after infusion was stopped.

Thus, esmolol can be administered to patients with severe left ventricular dysfunction. The beneficial effect (beta-adrenergic blockade) is usually achieved with small doses without clinically important hemodynamic changes. At larger doses, however, significant changes in biventricular function may be observed.

(J Am Coll Cardiol 1986;8:225–31)

Esmolol is a cardioselective beta-receptor blocker that has no intrinsic sympathomimetic activity and that is ultrashort-acting, with a 9 minute half-life. These desirable features make esmolol useful in the treatment of patients with ischemic heart disease (1,2). Previous studies in patients with preserved left ventricular function (1,2) show that this drug produces a modest depression in left ventricular function characterized by a slight increase in end-systolic volume, no change in end-diastolic volume, a slight increase in filling pressure and a decrease in ejection fraction, heart rate and cardiac output. However, the effects of esmolol in patients with left ventricular dysfunction are unknown. Because the candidates for use of esmolol may include patients with left ventricular dysfunction, this study was designed to examine the effects of incremental doses of esmolol in 10 patients with coronary artery disease and left ventricular dysfunction by using simultaneous hemodynamic and radionuclide angiographic measurements.

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Manuscript received October 31, 1985; revised manuscript received January 8, 1986, accepted February 18, 1986.

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Methods

Study patients. The study group consisted of 10 inpatients with a diagnosis of coronary artery disease and left ventricular dysfunction assessed by means of radionuclide angiography or contrast angiography; 9 of the 10 patients had had recent acute myocardial infarction (range 2 to 27 days, mean 11) and continued to have angina postinfarction; one (Case 3) had historic evidence of old myocardial infarction and was hospitalized because of severe angina pectoris. Five patients had Q wave infarction and five non-Q wave infarction. The site of infarction was anterior in seven patients, both anterior and inferior in two patients and undetermined in one patient. Of the seven patients who underwent coronary arteriography, six had multivessel disease and one had one vessel disease. None of the patients had clinical evidence of congestive heart failure. All patients had a baseline systolic blood pressure of 110 mm Hg or more and a heart rate of 70 beats/min or more; none had

0735-1097/86/$3.50

atrioventricular block greater than first degree, intolerance to beta-adrenergic blocking drugs, severe renal or hepatic disease, chronic obstructive pulmonary disease or bronchial asthma. Beta-blockers, verapamil and diltiazem were discontinued for a minimum of two half-lives; none of the patients was being administered nitroglycerin intravenously and none was receiving a digitalis preparation. It should be noted that two half-lives of drug washout may not be sufficient to rid the patient completely of beta-blockers, verapamil or diltiazem.

The patients agreed to participate in the study; each had signed a consent form that had been approved by the Institutional Review Board of the hospital. There were no complications.

Hemodynamic measurements. On the day of the study a balloon-tipped thermodilution catheter, inserted percutaneously through a femoral vein or an antecubital vein, was used to measure the pulmonary artery wedge pressure, pulmonary artery pressure, right atrial pressure and cardiac output. The systemic pressure was monitored with a 5F 10 inch (25.4 cm) Teflon catheter or an 8F pigtail catheter inserted percutaneously into a femoral artery. All pressures were recorded on a multichannel Electronics for Medicine recorder (3). The cardiac output was obtained in triplicate. The hemodynamic measurements were obtained at baseline, at each titration dose and 10 to 30 minutes after termination of the infusion.

Radionuclide angiography. Equilibrium cardiac gated blood imaging was performed with an in vivo red blood cell labeling technique. Technetium-99m pertechnetate (20 mCi) was used for labeling (4). The images were acquired with a mobile Anger gamma camera (Technicare series 420) fitted with a low energy all-purpose parallel-hole collimator, and the energy photopeak was centered at 140 keV with a 20% window. Each study was obtained in a modified left anterior oblique projection (30 to 45°) that best separated the left ventricular and right ventricular chambers with a caudal tilt whenever necessary. Sixteen frames per RR interval were acquired into a 64 × 64 matrix size, with an arrhythmic rejection of intervals beyond the 20% window.

For image data analysis, images were filtered by a nine point spatial smoothing technique and a temporal smoothing algorithm. The background subtraction was applied by a background region of interest adjacent and posterolateral to the left ventricle. The borders of the left ventricular (and then the right ventricular) chambers were determined by a semiautomatic quadrant threshold method. The background-corrected time-activity curve was derived from the left and right ventricles.

The ejection fraction was calculated as follows: (end-diastolic counts − end-systolic counts) / end-diastolic counts × 100. All studies were performed by one experienced observer; there was 2 ± 2% variability in sequential measurements. From the stroke volume measurement (by the thermodilution method) and the ejection fraction (by radionuclide angiography), the end-diastolic volume was calculated as stroke volume × ejection fraction. The end-systolic volume was calculated as end-diastolic volume − stroke volume (3).

Infusion of esmolol. Esmolol in a concentration of 10 mg/ml was infused intravenously with an infusion pump. Incremental doses of esmolol were given: 2, 4, 8, 12 and 16 mg/min. The 16 mg/min dose in a patient weighing 80 kg is comparable with an infusion rate of 200 μg/kg per min. The infusion at each dose was continued for 5 minutes; a bolus injection of either 10 or 20 mg of esmolol was also given into the injection port before each titration step. At the end of each titration period, simultaneous hemodynamic and radionuclide angiographic measurements were made (Table 1). Finally, 10 to 30 minutes after the infusion ceased, these measurements were repeated. All patients tolerated the full titration schedule without side effects.

Statistical analysis. Analysis of variance with repeated measures was employed to study the group effects (patients with baseline left ventricular ejection fraction <25% and patients with baseline left ventricular ejection fraction 25 to 36%) for clinical (heart rate and systemic pressure) and some selected hemodynamic variables. A paired *t* test was then used for these variables to study the changes from baseline for all patients at each study period (titration periods and postinfusion period). All statistical analyses were performed using version 4.10 of the statistical programs from Statistical Analysis System (SAS Institute Inc., SAS User's Guide, 1982 ed.). The results of statistical tests were assessed using

Table 1. Design of Hemodynamic and Radionuclide Angiographic Measurements During and After Esmolol Infusion

		Esmolol (mg/min)					
	Baseline	2	4	8	12	16	Postinfusion
Hemodynamics*	+	+	+	+	+	+	+
RNV†	+	−	−	+	−	+	+
Bolus of esmolol (mg)	−	10	10	20	20	20	−

*Includes measurements of heart rate, aortic pressure, pulmonary artery wedge pressure, pulmonary artery pressure, right atrial pressure and cardiac output. †In six patients a radionuclide ventriculogram (RNV) was also obtained at an infusion rate of 8 mg/min. + = data were obtained; − = data were not obtained.

Table 2. Effects of Esmolol on Mean Heart Rate, Systemic Blood Pressure and Rate-Pressure Product in 10 Patients

		Esmolol (mg/min)					
	Baseline	2	4	8	12	16	Postinfusion
HR	91 ± 4	85 ± 4*	83 ± 4*	80 ± 3*	79 ± 4*	79 ± 3*	88 ± 4*
SBP	133 ± 5	130 ± 5	128 ± 5*	126 ± 5*	127 ± 5*	125 ± 5*	127 ± 5*
DBP	73 ± 2	72 ± 2	72 ± 2	70 ± 2	73 ± 3	72 ± 3	74 ± 4
MBP	95 ± 2	93 ± 2	93 ± 2	91 ± 2	94 ± 2	94 ± 2	92 ± 2
RPP ($\times 10^3$)	12 ± 0.5	11 ± 0.5*	10.6 ± 0.3*	10.1 ± 0.4*	9.9 ± 0.4*	9.7 ± 0.3*	11 ± 0.4*

*$p < 0.05$ versus baseline. DBP = diastolic blood pressure (mm Hg); HR = heart rate (beats/min); MBP = mean systemic pressure (mm Hg); RPP = rate-pressure product (heart rate × systolic blood pressure); SBP = systolic blood pressure (mm Hg).

the 0.05 level of significance and the results are expressed in some tables as mean ± SEM when appropriate.

Results

There were nine men and one woman between the ages of 47 and 70 years (mean 58). In the baseline study, the left ventricular ejection fraction was less than 25% in five patients and 25 to 36% in five patients. Because there were no significant differences in the drug effect between these two groups, the subsequent data were analyzed for the entire group of 10 patients. All patients had severe ventricular asynergy by radionuclide angiography, but none had discernible aneurysm and none had significant mitral regurgitation by clinical evaluation and by cardiac catheterization.

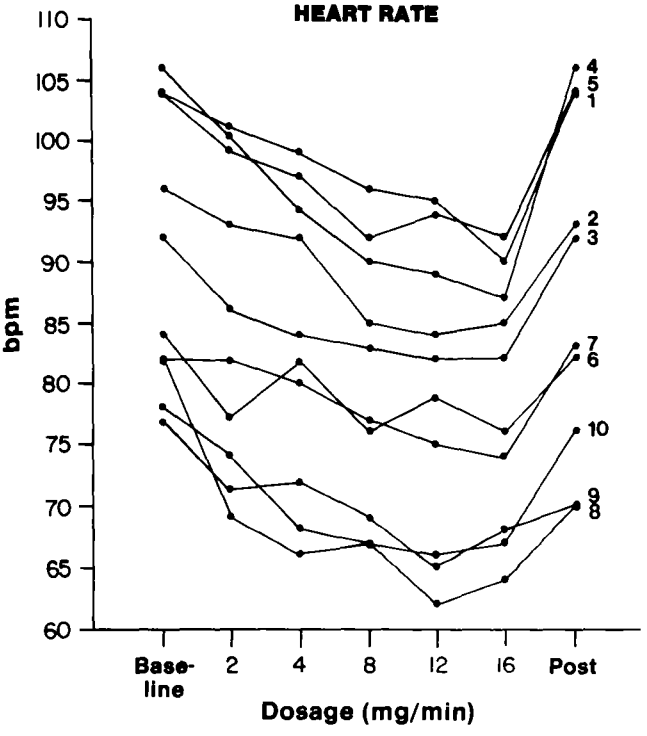
Effect of esmolol on heart rate and systemic pressure (Table 2, Fig. 1 and 2). A significant decrease in the mean heart rate of the group was noted starting at a dose of 2 mg/min, and a significant decrease was noted in systolic aortic pressure at a dose of 4 mg/min.

Effect of esmolol on hemodynamic measurements (Table 3, Fig. 3 and 4). Esmolol produced an increase in pulmonary artery wedge pressure, mean pulmonary artery pressure and mean right atrial pressure, as well as a decrease in cardiac output accompanied by an increase in systemic vascular resistance. The decrease in cardiac output was predominantly due to a decrease in heart rate because there was no significant change in the stroke volume (Table 3, Fig. 3 and 4). The changes in the hemodynamic measurements were variable; for example, at peak infusion Patients 2, 3 and 5 had a 5 mm Hg or more increase in pulmonary artery wedge pressure, whereas the remaining patients had a less than 5 mm Hg change. Similarly, Patients 7 and 9 had a 1 liter/min or more decrease in cardiac output, whereas the remaining patients had changes in the range of 0.5 liter/min. In general, the hemodynamic abnormalities were more pronounced at the higher doses.

Effect of esmolol on left ventricular ejection fraction (Table 4, Fig. 5 and 6). In the last six patients (Cases 5 through 10), ejection fraction measurements were also available at an infusion rate of 8 mg/min. At peak infusion, esmolol produced a decrease in left ventricular ejection fraction associated with an increase in end-diastolic volume and end-systolic volume. Because esmolol also produced a decrease in systolic pressure, the ratio of systolic pressure to end-systolic volume decreased with esmolol administration. As with the changes in hemodynamic measurements, the changes in the ejection fraction and volume showed considerable individual variability; for example, Patients 4, 8, 9 and 10 had a less than 5% decrease in ejection fraction, whereas Patients 1, 2, 3, 5, 6 and 7 had a 5% or more decrease.

Esmolol also decreased right ventricular ejection fraction (Table 4, Fig. 7). Table 4 also shows that at a dose of 8

Figure 1. Individual changes in heart rate with esmolol infusion in 10 patients. Post = 10 to 30 minutes after cessation of infusion.



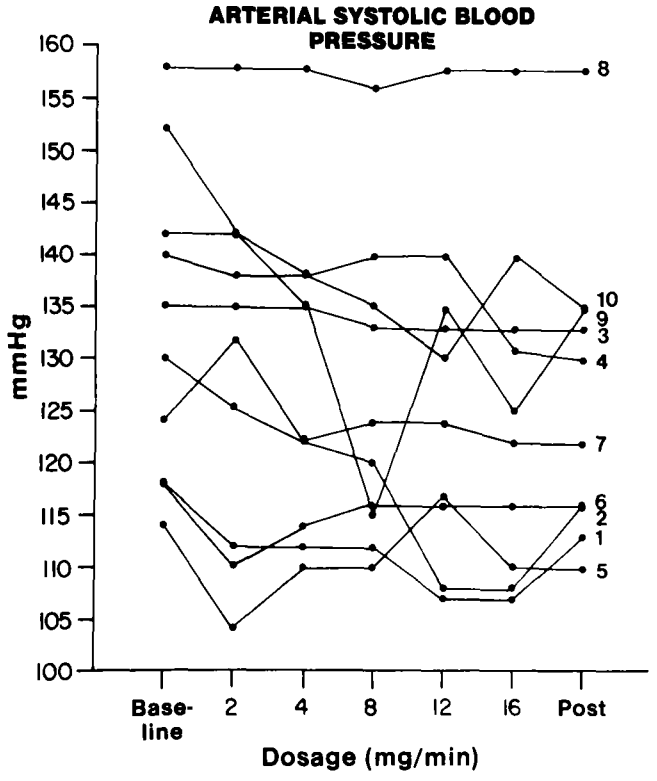


Figure 2. Individual changes in arterial systolic pressure with esmolol infusion in 10 patients.

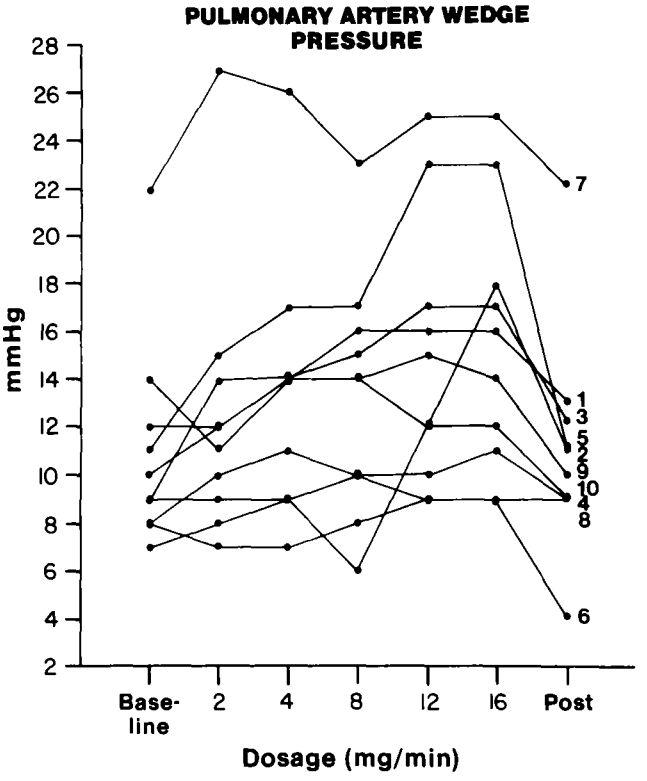


Figure 3. Individual changes in mean pulmonary artery wedge pressure with esmolol infusion in 10 patients.

mg/min, the changes in ejection fraction are less marked than those observed at a dose of 16 mg/min.

Discussion

Effects of esmolol. This study shows that esmolol produces beta-receptor blockade at small doses (2 to 4 mg/min) and that with increasing dosage, the beta-blockade is associated with further depression in left ventricular and right ventricular function. Of note is the individual variability in changes in heart rate, systemic pressure, pulmonary artery wedge pressure, pulmonary artery pressure, right atrial pressure, cardiac output, left ventricular ejection fraction and right ventricular ejection fraction. The depression in left ventricular function was also characterized by increases in both end-diastolic and end-systolic volumes. This is potentially a harmful effect because the left ventricular size is an important component determining wall stress, which in turn determines the myocardial oxygen demand. However, a reduction in systolic arterial pressure produced by esmolol,

Table 3. Effects of Esmolol on Mean Cardiac Hemodynamic Measurements in 10 Patients

		Esmolol (mg/min)					
	Baseline	2	4	8	12	16	Postinfusion
PAW	11 ± 1	13 ± 2	14 ± 2*	13 ± 2*	15 ± 2*	15 ± 2*	11 ± 1
PA	17 ± 2	19 ± 1	19 ± 2*	21 ± 2*	20 ± 2*	22 ± 2*	18 ± 2
RA	8 ± 1	8 ± 1	8 ± 1	9 ± 1	9 ± 1	10 ± 1*	8 ± 1
CO	4.9 ± 0.3	4.7 ± 0.3*	4.5 ± 0.3	4.4 ± 0.2*	4.3 ± 0.3*	4.3 ± 0.3*	4.7 ± 0.3*
SVI	30 ± 2	31 ± 3	30 ± 3	30 ± 2	30 ± 2	30 ± 2	30 ± 2
SVR (10^2)	15 ± 1.7	15.2 ± 1	15.5 ± 1.3*	15.7 ± 1.4*	16.4 ± 1.2*	16.9 ± 1.2*	15 ± 1.5

*$p < 0.05$ versus baseline. CO = cardiac output (liters/min); PA = mean pulmonary artery pressure (mm Hg); PAW = mean pulmonary artery wedge pressure (mm Hg); RA = mean right atrial pressure (mm Hg); SVI = stroke volume index (ml/beat per m^2); SVR = systemic vascular resistance (dynes·s·cm^{-5}).

Table 4. Effects of Esmolol on Left Ventricular Ejection Fraction and Volume and Right Ventricular Ejection Fraction (mean data)

	Baseline (n = 10)	8 mg/min (n = 6)	16 mg/min (n = 10)	Postinfusion (n = 10)
LVEF (%)	27 ± 2	25 ± 2*	21 ± 2*	27 ± 2
LVEDV (ml)	210 ± 21	250 ± 29*	266 ± 20*	211 ± 23
LVESV (ml)	155 ± 17	189 ± 27*	211 ± 19*	157 ± 20
RVEF (%)	38 ± 2	32 ± 2*	29 ± 2*	38 ± 2

*$p < 0.05$ versus baseline. LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RVEF = right ventricular ejection fraction.

which is also a determinant of wall stress, may offset the harmful effect of the increase in end-systolic volume. The depression in left ventricular function was less marked at a dose of 8 mg/min than that observed at 16 mg/min. It is possible, therefore, that the dose of esmolol can be titrated in an individual patient to produce the desired beta-blockade as indicated by reduction in the heart rate-systolic pressure (double) product without significant deterioration in left ventricular function. Significant reduction in the rate-pressure product was accomplished at a dose of 4 mg/min and a 20% reduction was obtained with 16 mg/min.

Changes in systemic vascular resistance. Esmolol appears to have no direct effect on the peripheral vasculature; systemic vascular resistance increased to compensate for the decrease in cardiac output. This rise in systemic vascular resistance was not great, allowing the central aortic pressure to decline which is important in successfully reducing myocardial oxygen demand even in patients with severe left ventricular dysfunction.

Side effects. Despite hemodynamic deterioration after administration of esmolol, all patients tolerated the full titration schedule without angina pectoris, dyspnea or excessive decreases in systemic pressure or heart rate. However, it should be mentioned that our patients, despite left ventricular dysfunction, showed no signs of overt heart failure; their mean left ventricular filling pressure was in the normal

Figure 4. Individual changes in cardiac output with esmolol infusion in 10 patients.

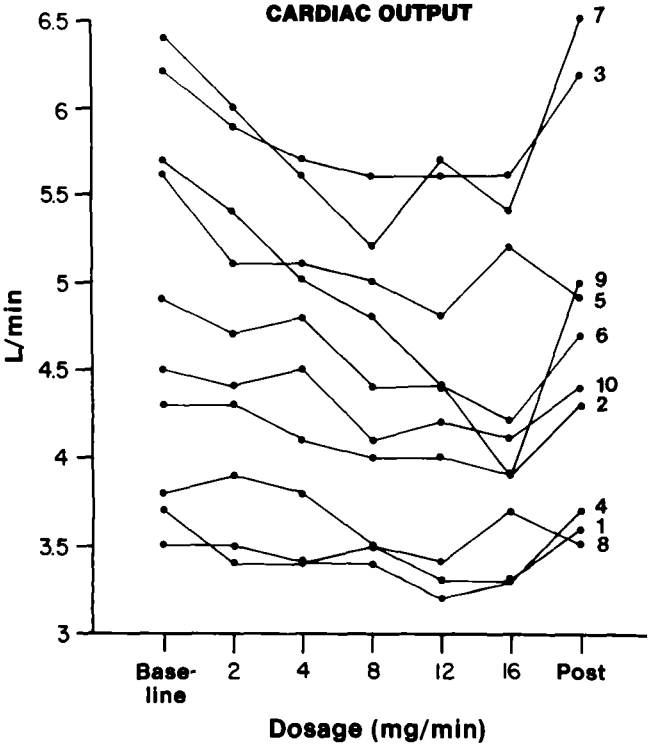
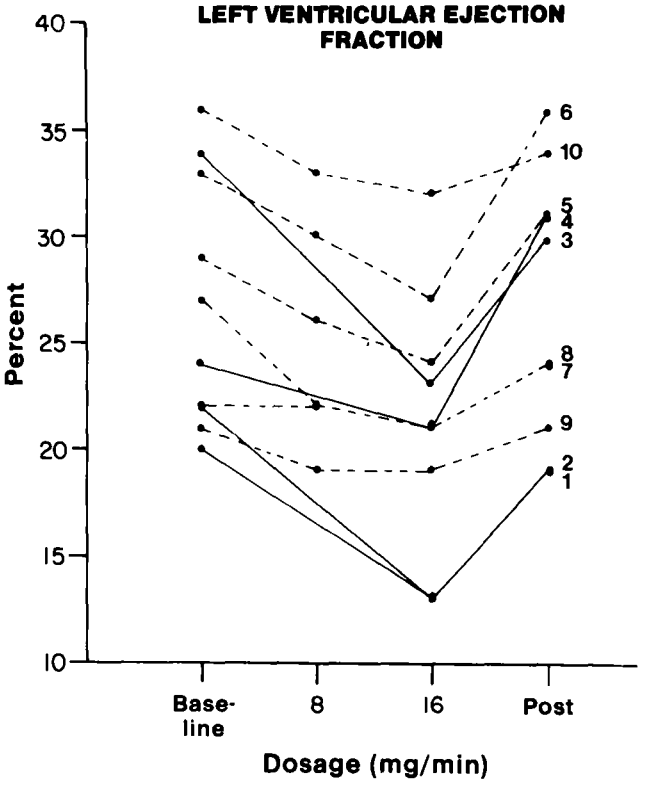


Figure 5. Individual changes in left ventricular ejection fraction with esmolol infusion in 10 patients. In Patients 5 to 10 (**dashed lines**) the ejection fraction was also measured at a dose of 8 mg/min.



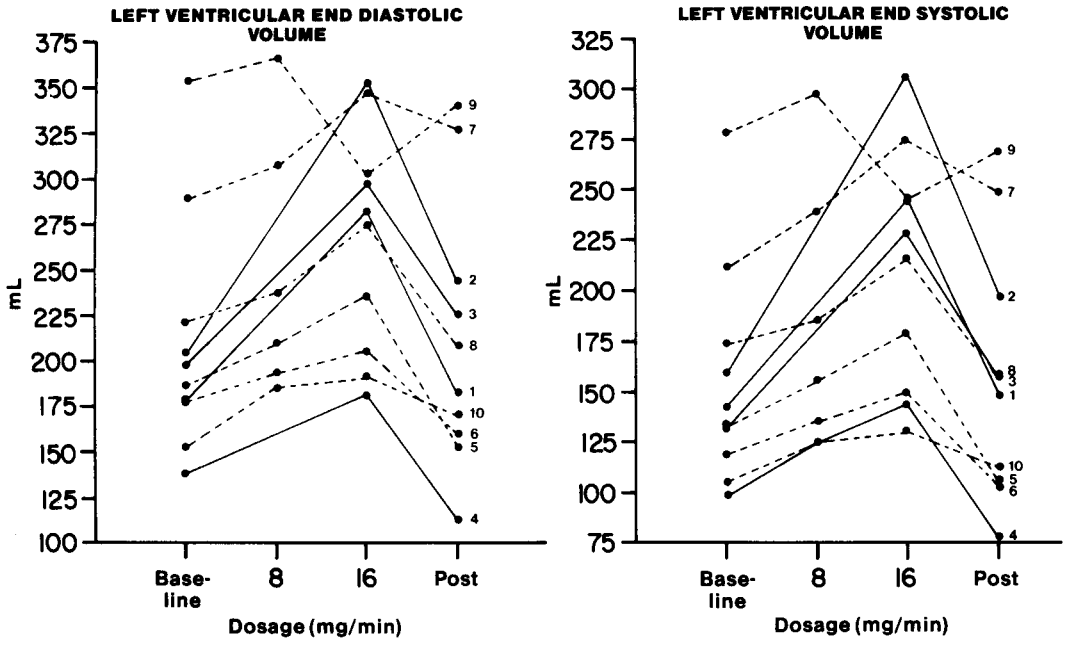


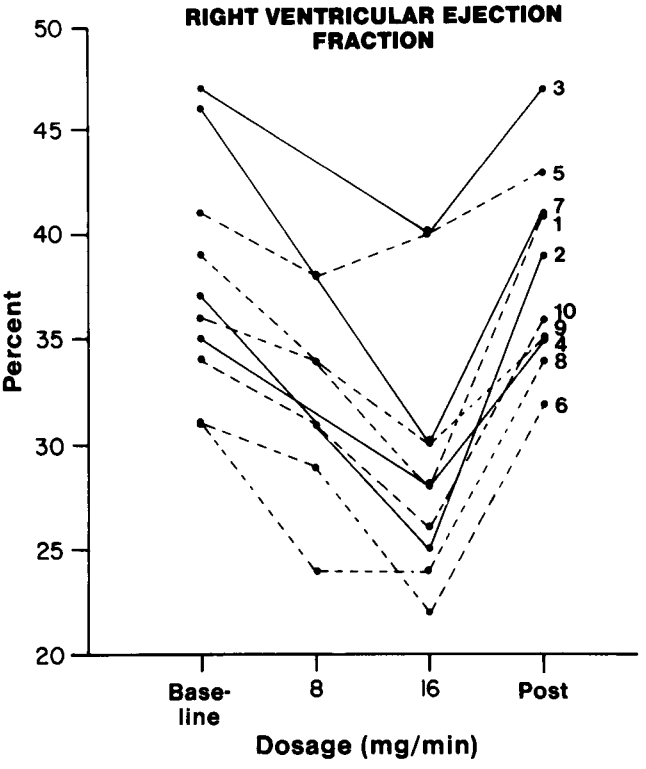
Figure 6. Individual changes in left ventricular end-diastolic (**left**) and end-systolic (**right**) volume with esmolol infusion (format as in Fig. 5).

range. The fact remains that in some patients a significant elevation in left ventricular filling pressure and a deterioration in ejection fraction were observed in the absence of symptoms. This suggests that bedside hemodynamic monitoring may be necessary, especially if higher doses of esmolol are used.

Effects of esmolol on right ventricular function. The depression in right ventricular function is probably due to two mechanisms, one direct and one due to an increase in afterload as a result of the increase in pulmonary artery pressure and right ventricular volume (5).

Clinical implications. This study confirms previous studies indicating that esmolol has a short duration of action; most of the hemodynamic measurements returned toward baseline 10 to 30 minutes after infusion was stopped. The short duration of action of this intravenous beta-blocker makes it useful in the management of patients with ischemic heart disease; for example, the control of angina pectoris in postinfarction patients or in those with unstable angina pectoris, or control of arrhythmias and hypertension in postoperative patients (6,7). Further studies are necessary in patients with more severe left ventricular dysfunction because such dysfunction, although evident, was not very marked in our study patients. Only one patient had a pulmonary artery wedge pressure above 14 mm Hg, and none had a left ventricular ejection fraction less than 20%. Because this study examined the acute effects of esmolol, further studies are necessary to evaluate the effects of prolonged periods of infusion as well as the interaction between esmolol and other cardiac medications, such as nitrates, digitalis and calcium channel blockers, that may be used concurrently in the same patients.

Figure 7. Individual changes in right ventricular ejection fraction with esmolol infusion in 10 patients (format as in Fig. 5).



We thank Angela Parmley and Valerie Wakefield for secretarial assistance in the preparation of this manuscript. We also thank Edith Schwager for editorial assistance.

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